## REMARKS

On page 1 of the Advisory Action, the Examiner states that the Response After Final filed November 16, 2001 will be entered, but, as discussed in more detail below, is not sufficient to overcome the outstanding rejections.

In paragraph 2 on page 2 of the Advisory Action, the Examiner indicates that the Substitute Specification filed November 16, 2001 has been entered.

In paragraph 3 on page 2 of the Advisory Action, the Examiner maintains the rejection of Claim 10 under 35 U.S.C. § 112, first paragraph as lacking written description in the original specification.

Specifically, the Examiner appears to contend that there is no written description in the specification for the expression "**in the range** of 6.5 Gy to 7.0 Gy" because such would include 6.0, which is insufficient.

Applicants respectfully submit that this is an improper reading of Claim 10. Claim 10 is dependent on Claim 9. Claim 9 recites "at least 6.5". Since a dependent claim necessarily limits an independent claim, is it clear that Claim 10 can not cover a Gy below "at least 6.5" as recited in Claim 9, i.e., Claim 10 can not cover a Gy of 6.0 as contended by the Examiner.

Nonetheless, the Examiner advised during a teleconference interview on December 31, 2001, that this rejection has been maintained in view of the expression "in the range of", and the deletion of the expression will overcome the rejection. Solely, to advance prosecution, Applicants hereby amend Claim 10 to delete "in the range of" as suggested by the Examiner. Thus,

Applicants respectfully submit that the Examiner's rejection has been rendered moot.

Finally, in paragraph 4 on pages 2-3 of the Advisory Action, the Examiner maintains the rejection of Claims 9-12 under 35 U.S.C. § 112, first paragraph. Specifically, the Examiner states that while the specification is enabling for inducing immunotolerance in a mouse, such is not enabling for inducing immunotolerance in larger transplant recipients, such as a human.

The Examiner notes Applicants' argument that because the irradiation dose is presented in grays (i.e., the absorbed dose), the results of the mouse experiments are applicable to a human transplant, irrespective of body mass. However, the Examiner contends that even when the dose delivered is normalized between different species, the *response to that dose* is not the same, because there are differences between human and mouse bone marrow cells in terms of radiation sensitivity. Hence, the Examiner concludes that in the absence of direction to experimental readouts that are reasonably predictive that a particular sublethal dose leads to graft survival, it would require undue experimentation, particularly in humans, to establish an effective irradiation dose based solely upon the end readout of graft survival.

For the following reasons, Applicants respectfully traverse the Examine's rejection.

Even assuming *arguendo* that there are differences between human and mouse bone marrow cells in terms of radiation sensitivity, Applicants respectfully submit that one skilled in the art would expect that human bone marrow cells have a

relatively higher radiation sensitivity than mouse bone marrow cells. Bone marrow cells having a higher radiation sensitivity receive a higher level of damage from a specific radiation dose. When the recipient receives a higher level of damage to the bone marrow cells, the graft rejection action of the recipient is reduced, i.e., the rejection response occurring by recognizing, for example, the transplanted skin of a graft donor as an allogenic substance, is inhibited.

Therefore, one skilled in the art would appreciate that a human should exhibit a higher level of successful skin engraftment than a mouse when both are subjected to irradiation with the same level of radiation dose, because a human has higher radiation sensitivity than a mouse. In other words, immunological tolerance can be more successfully established in humans than in a mouse. The skilled artisans would readily understand from the present specification that graft rejection will be reduced when the recipient receives a higher level of radiation dose or the recipient exhibits higher radiation sensitivity, and thus successful engraftment of the transplanted cells (an engraftment rate of 100% after transplantation) can be readily achieved and immunological tolerance necessary for organ transplantation can be successfully established based on the teachings in the present specification.

Hence, Applicants respectfully submit that it is unreasonable for the Examiner to maintain the rejection on the basis that "because human and mouse bone marrow cells are different in terms of radiation sensitivity, the present specification does not enable those skilled in the art to

predict that a particular sublethal dose which leads to graft survival in a mouse could be effective in humans".

Moreover, when the recipient is subjected to the specific irradiation method (total body irradiation) of the present invention, not only bone marrow cells, but also all other cells, tissues and organs of the recipient have a risk of receiving damage. For reasons of safety against radiation exposure, the level of radiation dose to a human should be as low as possible. Even when successful engraftment of, e.g., skin, is assured, it can not be practically used as a therapeutic method if the recipient suffers from adverse side-effects, such as death caused by receiving damage to other organs, etc.

Prior to the present invention, experiments on total body irradiation of humans using a radiation dose at 6.5-7.0 Gy, and even higher, had been successfully carried out in the art. Thus, one skilled in the art would know that a radiation dose of 6.5-7.0 Gy, as claimed in the present specification, is not lethal, but is safe to humans, i.e., such is a sublethal dose (see Clift et al, *Blood*, 76(9):1867-1871; a copy of which is attached hereto).

More specifically, as shown in the left column on page 1867 of Clift et al, between 1976 and 1978, 9.2 Gy of total body irradiation (TBI) was performed in human patients with acute myeloid leukemia (AML) by the Seattle Marrow Transplant Team. Under the heading of "MATERIALS AND METHODS", it describes that "all patients were randomized to receive either 12.0 Gy or 15.75 Gy of TBI before transplantation".

Thus, before the present application was filed, it had been widely known by those skilled in the art that a 6.5 Gy-7.0 Gy of TBI is by no means dangerous to a human.

Hence, based upon the mouse data in the specification, it is reasonably predicted by the skilled artisans that a sublethal radiation dose as set forth in Claims 9-10, specifically, at least 6.5 Gy, and 6.5-7.0, respectively, which leads to graft survival in a mouse, would be effective in a human. Thus, Applicants respectfully submit that the present specification clearly enables effectively inducing immunotolerance in a human and other mammals.

Accordingly, Applicants respectfully submit that the claims are enabled by the present specification, and thus request withdrawal of the Examiner's rejection.

In view of the amendment to Claim 10, and the arguments set forth above, reexamination, reconsideration and allowance are respectfully requested.

The Examiner is invited to contact the undersigned at the telephone number listed below on any questions that might arise.

Respectfully submitted,

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Date: January 16, 2002

## A P P E N D I X

Marked-Up Version of Changes

**IN THE CLAIMS:**

Claim 10 is being amended as follows:

Claim 10. (Amended) The method according to Claim 9, wherein said sublethal radiation dose is [in the range of] 6.5 Gy to 7.0 Gy.